Alterations in White Matter Microstructure Are Associated with Goal-Directed Upper-Limb Movement Segmentation in Children Born Extremely Preterm

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Abstract: Altered white matter microstructure is commonly found in children born preterm (PT), especially those born at an extremely low gestational age (GA). These children also commonly show disturbed motor function. This study explores the relation between white matter alterations and upper-limb movement segmentation in 41 children born PT (19 girls), and 41 children born at term (18 girls) at 8 years. The PT group was subdivided into extremely PT (E-PT; GA = 25–27 weeks, $N = 10$), very PT (V-PT; GA = 28–32 weeks, $N = 13$), and moderately PT (M-PT; GA = 33–35 weeks, $N = 18$). Arm/hand preference (preferred/non-preferred) was determined through object interactions and the brain hemispheres were designated accordingly. White matter alterations were assessed using diffusion tensor imaging in nine areas, and movement segmentation of the body-parts head, shoulder, elbow, and wrist were registered during a unimanual goal-directed task. Increased movement segmentation was demonstrated consistently on the preferred side in the E-PT group compared with the term born group. Also compared with the term born peers, the E-PT group demonstrated reduced fractional anisotropy (FA) in the cerebral peduncle (targeting the corticospinal tract) in the hemisphere on the non-preferred side and in the splenium of corpus callosum. In contrast, in the anterior internal capsule on the preferred side, the E-PT group had increased FA. Lower FA in the cerebral peduncle, but higher FA in the anterior internal capsule, was associated with increased movement segmentation across body-parts in a contralateral manner. The results suggest that impaired development of sensorimotor tracts in E-PT children could explain a sub-optimal spatiotemporal organization of upper-limb movements. *Hum Brain Mapp* 38:5051–5068, 2017. © 2017 Wiley Periodicals, Inc.

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INTRODUCTION

Extensive empirical findings show that a preterm (PT) birth is associated with increased risk of neurodevelopmental disabilities and impairments [Blencowe et al., 2013], including white matter aberrations related to functional deficits [Li et al., 2015; Pannek et al., 2014]. Studies of the PT infant brain suggest that abnormalities in brain development are characterized by reduced maturity of the cerebral cortex, seemingly due to the disruption of neural connectivity rather than to a reduced number of cortical neurons [Pannek et al., 2014]. Increased knowledge on how white matter microstructure relates to movement abilities is important to further the understanding of the neural basis of motor functions and the mechanisms involved in a deviant neuromotor development associated with a PT birth. Thus, the present study utilizes the combination of neuroimaging measures with high-resolution movement registration to improve such understanding.

Diffusion tensor imaging (DTI) is a tool for evaluating white matter impairments in the brain, and in particular, the diffusion parameter fractional anisotropy (FA) is usually a good measure of white matter integrity [Alexander et al., 2007]. Alterations in cerebral FA are associated with prematurity [Allin et al., 2011; Kelly et al., 2016]; however, importantly, the alterations in FA are not homogenous throughout the PT brain. A recent meta-analysis (based on 13 studies, including 513 participants in total) reported decreased FA in children born PT compared with controls born at term in parts of the splenium and genu of corpus callosum, external capsule, posterior internal capsule, superior fronto-occipital and longitudinal fasciculus, posterior thalamic radiation, cingulum, and the posterior corona radiata, but increased FA in other parts of the posterior corona radiata and the anterior corona radiata [Li et al., 2015]. Depending on the developmental stage, white matter changes in the PT brain in terms of FA seem to vary not only across brain tracts, but also within tracts. In addition, interpretation of FA in terms of underlying pathology is not straightforward, as FA depends heavily on the fiber architecture in question, which in turn, depends on brain localization [Groeschel et al., 2014].

Changes in white matter areas/tracts have been shown to correlate with different behavioral outcomes in childhood [De Bruine et al., 2013; Drobyshevsky et al., 2007; Hüppi et al., 1998], but there is great variability in severity outcomes, and data are still limited for the population of children born PT. The majority of the studies have investigated associations between cerebral diffusion parameters measured during the neonatal period and later

neurodevelopmental outcomes. For instance, white matter changes in occipital and cerebellar regions in early infancy have been found to have lasting negative associations with motor and executive functioning in children born PT at early school-age [Thompson et al., 2014]. However, less is known about changes in subcortical white matter and their relations to motor functions in children born PT at early childhood. A region that is especially vulnerable to injury following a premature birth is the periventricular area through which the sensorimotor pathways for the extremities pass [Kuban et al., 2001]. Consequently, movement difficulties affecting the arms and legs are frequent following brain injury in infants born prematurely [Cioni, 2003]. Further, even without evident neonatal brain injuries, children born very PT and/or with very low BW are at increased risk for long-term motor impairment [De Kieviet et al., 2009], including reduced fine motor skills [Bos et al., 2013].

Previous studies of sensorimotor performance in children demonstrate that three-dimensional (3D) movement registration is a reliable measurement method and the derived analyses are useful for detailed characterization of movement abilities and asymmetries—even in neonates and infants—and also sensitive to age-related changes [Johansson et al., 2014; Rönnqvist and Domellöf, 2006]. The 3D motion analysis provides the spatiotemporal attributes of movement trajectories and segmentation, which is essential for understanding the nature of movement control. Still, few studies have used 3D motion analysis to investigate early sensorimotor control in infants and children, especially those with a premature birth. Motion analyses of reaching movements and visuo-manual aiming have shown promising results in characterizing the influence of premature birth on movement control, distinguishing between minor movement coordination problems and in identifying subtle sensorimotor impairments [Fallang et al., 2003; Johansson et al., 2014; Sagnol et al., 2007; Toledo and Tudella, 2008; Van Braeckel et al., 2008]. At preschool- and early school age, significant differences between children born very PT and those born at term regarding movement smoothness and segmentation have been demonstrated [Johansson et al., 2014]. Studies using 3D motion analysis involving children born PT have also reported less evident functional lateralization in terms of less apparent side differences during upper-limb performance compared with term born controls [Johansson et al., 2014; Rönnqvist and Domellöf, 2006]. Indeed, whilst approximately 90% of typically developing school children manifest a right hand preference [Szaflarski et al., 2012], a recent meta-analysis suggests that the rate of right-hand

preference is lower among children born PT (63%–92%), even in cases where no developmental deviation is present [Domellöf et al., 2011]. As functional lateralization, for example, as expressed in hand preference, is an important aspect of sensorimotor development in relation to hemispheric organization, this phenomenon warrants further exploration.

To our knowledge, no previous study has investigated the associations between diffusion alterations in white matter and upper-limb spatiotemporal movement parameters derived from 3D motion analysis and/or functional lateralization in children born either at term or PT. By studying these associations in children born PT in comparison to term born children, a more comprehensive understanding can be attained of how a PT birth influences the developing brain and movement control. In this study, we aim to specifically examine if movement segmentation in goal-directed upper-limb movements at early school age vary between term born children and, based on gestational age, subgroups of children born PT. Additionally, we explore if differences in diffusion parameters of white matter can explain variations in movement segmentation and laterality indices.

MATERIALS AND METHODS

Participants

The original sample consisted of 130 children (term born: $N = 69$, mean age = 7.8 years, 31 F/38 M; PT: $N = 61$, mean age = 7.8, 24 F/37 M). The children born PT were recruited through records from the neonatal intensive care unit of Norrland's University Hospital, Umeå, Sweden, and the age-equivalent children born at term via birth records from the maternity ward at the same hospital. All term born children were healthy at birth according to ICD-10 and they were devoid of (known) genetic and/or congenital abnormalities. Parents were contacted via mail, followed by telephone contact, and inquired if they were interested in their child being enrolled in the study.

The children underwent 3D movement registration and laterality assessment [Johansson et al., 2014]. Two term born children were excluded; one due to epilepsy and the other due to inability to perform the motoric test battery. The remaining 128 participants were invited to undergo a MRI examination including DTI whereof 89 agreed (43 PT and 46 term born). A mock MRI training session preceded the actual examination in order to familiarize the children with the MRI environment. Those who declined the MRI examination (18 PT and 21 term born) did not differ significantly from the participating children with regard to medical and demographic features (age, gestational age [GA], birth weight [BW], parental education, and for the children born PT: Apgar score, head circumference at birth and medical risk factors in the perinatal period). Neither did they significantly differ from those participating in terms

of spatiotemporal movement segmentation. Seven children were excluded from the post-examination DTI analysis due to the following: motion artifacts (term born = 1), cerebral pathology in the control group (term born = 3), and aborted MRI examination due to discomfort (PT born = 2; term born = 1). Thus, the final sample consisted of 82 children, 41 PT (18 F/23 M) and 41 term born (19 F/22 M). The PT group was further subdivided into extremely PT (E-PT, GA = 25–27 weeks, $N = 10$), very PT (V-PT, GA = 28–32 weeks, $N = 13$), and moderately PT (M-PT, GA = 33–35 weeks, $N = 18$). One of the children born V-PT in the final sample was diagnosed with cerebral palsy, but did not deviate in test performance from the other children born V-PT; hence, the child was included in the analyses. See Table I for the demographics of the participating children.

Ethical approval for the study was obtained from the Umeå Regional Ethical Review Board, and the study was performed in agreement with the Declaration of Helsinki. All children gave assent for participating in the study, and written, informed consent for participation was obtained from their parents.

Behavioral Outcome Measures

Laterality preferences

Laterality preferences of the hand, foot, and eye were assessed through repeated observation of the side that the child selected during interaction with different objects or when performing a task. The assessment was based on modified versions of the Edinburgh Handedness Inventory and Coren and Porac's laterality questionnaire [Coren and Porac, 1980; Oldfield, 1971]. Handedness was assessed by observing which hand the child used when interacting with five common objects (i.e., drawing, cutting with scissors, hammering, throwing a small ball, opening boxes), and foot/leg preference was assessed through three tasks by observation of which foot/leg that was chosen for interaction (kicking a ball, side of initiation when walking, and side chosen when standing on one leg). The eye preference was determined from the eye that was selected when looking through a kaleidoscope. When objects were used, they were always presented at the child's midline and, in all tasks, both sides had to be in a similar neutral, non-engaged position, that is, both feet aligned on the floor in kicking or stepping tasks. Each action was repeated at least three times. An index was calculated for the hand, foot and eye separately and in total by the equation $(\#R - \#L)/(\#R + \#L)$, where $\#R/L$ denotes the number of times the child acted with the respective side. Negative values (−0.3 to −1.0) represented a left side preference and positive values (0.3–1.0) a right side preference. Values between −0.3 and 0.3 were defined as a non-evident side preference. See Table II for data of lateralization.

TABLE I. Clinical features and fractional anisotropy in the gestational groups

	Term	M-PT	V-PT	E-PT	<i>F</i> (3,78)	<i>P</i> -value
N	41	18	13	10	–	–
Gender (F/M)	19/22	8/10	5/8	5/5	–	–
Age (y)	8.1 (0.6) [7.0–9.2]	8.3 (0.8) [7.1–9.5]	8.3 (0.7) [7.2–9.3]	7.6 (0.7) [7.0–8.9]	1.3	0.27
GA (weeks)	40.2 (1.0) [38.0–41.9]	34.3 (0.5) [33.4–35.4]	30.7 (1.4) [28.3–32.7]	26.4 (0.9) [25.3–27.4]	698	<0.001 ^a
BW (g)	3700 (402) [1660–3130]	2274 (381) [1540–2962]	1480 (336) [1054–2106]	797 (121) [607–992]	249	<0.001 ^a
BL (cm)	51.3 (1.9) [49–57]	44.9 (2.0) [41–49]	39.9 (2.9) [35–46]	33.3 (1.7) [31–35]	136	<0.001 ^a
Head circumf. (cm)	35.4 (1.1) [33–39]	32.4 (1.4) [30–35]	28.5 (1.8) [26–32]	23.7 (1.1) [22–25]	254	<0.001 ^a
Ventr. width (mm)	32.8 (2.3) [27.4–38.0]	31.7 (2.7) [27.1–36.4]	34.2 (3.4) [28.4–41.1]	33.7 (1.8) [32.1–38.0]	3.0	0.037 ^a
Evans index	0.243 (0.013) [0.209–0.268]	0.239 (0.014) [0.211–0.262]	0.222 (0.024) [0.219–0.317]	0.258 (0.012) [0.238–0.282]	5.6	0.002 ^a
Apgar 10	9.4 (0.5) ^b [9–10]	8.9 (0.8) [7–10]	9.0 (0.6) [8–10]	8.3 (0.7) [7–9]	9.0	<0.001 ^a
Cerebral pathology^d (Yes/No)	NA ^c	NA ^c	6/7	5/5	–	NA ^e
IVH GR I–II (N)	–	–	4	1	–	–
IVH GR III+ (N)	–	–	1	0	–	–
PVL (N)	–	–	1	0	–	–
Mild abn. non-class. (N)	–	–	0	4	–	–
Mother's ed. (y)	14.0 (1.9) [11–18]	15.3 (2.3) [11–19]	13.0 (2.7) [9–17]	14.6 (2.9) [13–21]	2.6	0.06
Father's ed. (y)	13.7 (3.0) [9–20]	14.4 (3.0) [12–21]	13.0 (2.4) [9–17]	13.9 (2.7) [11–18]	0.6	0.63
ALIC L	0.54 (0.11)	0.53 (0.07)	0.55 (0.07)	0.58 (0.08)	0.55	0.65
ALIC R	0.50 (0.08)	0.52 (0.06)	0.45 (0.08)	0.53 (0.07)	2.53	0.063
PLIC L	0.75 (0.06)	0.76 (0.06)	0.75 (0.04)	0.78 (0.05)	1.05	0.38
PLIC R	0.72 (0.05)	0.73 (0.05)	0.71 (0.02)	0.73 (0.05)	0.66	0.58
PFC Lat L	0.35 (0.05)	0.38 (0.06)	0.38 (0.07)	0.35 (0.05)	1.93	0.13
PFC Lat R	0.34 (0.05)	0.35 (0.06)	0.35 (0.07)	0.37 (0.07)	0.90	0.45
PFC Ant L	0.37 (0.05)	0.37 (0.07)	0.38 (0.05)	0.36 (0.08)	0.21	0.90
PFC Ant R	0.37 (0.05)	0.36 (0.05)	0.38 (0.05)	0.35 (0.06)	0.80	0.50
OR L	0.55 (0.04)	0.56 (0.05)	0.56 (0.05)	0.52 (0.04)	3.03	0.034 ^a
OR R	0.53 (0.05)	0.55 (0.06)	0.53 (0.05)	0.49 (0.03)	3.08	0.032 ^a
SLF L	0.41 (0.05)	0.40 (0.06)	0.41 (0.04)	0.42 (0.05)	0.33	0.80
SLF R	0.40 (0.05)	0.39 (0.04)	0.38 (0.04)	0.39 (0.04)	0.48	0.70
ILF L	0.55 (0.07)	0.57 (0.06)	0.53 (0.09)	0.57 (0.05)	1.30	0.28
ILF R	0.51 (0.05)	0.55 (0.06)	0.51 (0.07)	0.54 (0.06)	2.21	0.09
MCP L	0.70 (0.08)	0.71 (0.06)	0.69 (0.11)	0.67 (0.08)	0.56	0.64
MCP R	0.68 (0.07)	0.68 (0.08)	0.68 (0.10)	0.66 (0.11)	0.91	0.97
CP L	0.75 (0.07)	0.78 (0.07)	0.74 (0.06)	0.73 (0.04)	1.46	0.23
CP R	0.71 (0.05)	0.72 (0.06)	0.70 (0.08)	0.68 (0.09)	0.90	0.44
CC genu	0.74 (0.07)	0.72 (0.07)	0.73 (0.08)	0.73 (0.07)	0.58	0.63
CC trunc	0.68 (0.09)	0.71 (0.09)	0.63 (0.10)	0.63 (0.10)	2.89	0.041 ^a
CC splen	0.81 (0.08)	0.81 (0.10)	0.79 (0.07)	0.72 (0.12)	2.76	0.048 ^a

Numbers represent mean with (SD) and [range] in brackets, *F*-value based on ANOVA (*F*), and the corresponding *P*-value. Gender is expressed as ratios. *Abbreviations*: Term, term born; M-PT, moderately preterm; V-PT, very preterm; E-PT, extremely preterm; N, number of children; F, females; M, males; GA, gestational age; BW, birth weight; BL, birth length; circumf, circumference (measured at birth); ventr, ventricular; IVH, intraventricular hemorrhage; GR, grade; PVL, periventricular leucomalacia; Mild abn. non-class., mild abnormality non-classifiable; ed., education length; L, left side; R, right side; ALIC, anterior limb of the internal capsule; PLIC, posterior limb of the internal capsule; PFC Lat, lateral prefrontal cortex; PFC Ant, anterior prefrontal cortex; OR, optic radiation; SLF, superior longitudinal fascicle; ILF, inferior longitudinal fascicle; MCP, middle cerebellar peduncle; CP, cerebral peduncle; CC genu, genu of corpus callosum; CC trunc, truncus of corpus callosum; CC splen, splenium of corpus callosum.

^aSignificantly different means based on ANOVA *F*-test (Bonferroni corrected).

^b*N* = 38.

^cNot assessed, not routinely examined in infants with a gestation period above 32 weeks *unless* clinically warranted. Thus, in no case was this warranted.

^dDiagnosed during care at the neonatal intensive care unit.

^eNot assessed.

TABLE II. Lateralization indices and movement segmentation in the gestational groups

	Term N = 41	M-PT N = 18	V-PT N = 13	E-PT N = 10	Statistics
Lat index hand R/NR	0.84 (−0.20 to 1.00) 38/3	0.72 (−0.76 to 1.00) 15/3	0.84 (−1.00 to 1.00) 8/5	0.60 (−0.76 to 0.92) 8/1/1/2	$\chi^2(3) = 6.5, P = 0.09^a$ $\chi^2(1) = 4.5, P = 0.03^b$
Lat index foot R/NR	0.33 (−0.73 to 1.00) 21/20	0.33 (−0.33 to 1.00) 10/8	0.20 (−0.73 to 0.87) 3/10	0.20 (−0.33 to 1.00) 4/6	$\chi^2(3) = 4.1, P = 0.25^a$ $\chi^2(1) = 0.8, P = 0.38^b$
Lat index eye R/NR	1.00 (−1.00 to 1.00) 27/14	1.00 (−1.00 to 1.00) 11/7	1.00 (−1.00 to 1.00) 9/4	0.00 (−1.00 to 1.00) 5/5	NA ^c $\chi^2(1) = 0.2, P = 0.64^b$
Lat index total R/NR	0.55 (−0.16 to 0.97) 26/15	0.46 (−0.30 to 1.00) 10/8	0.32 (−0.78 to 0.96) 8/5	0.30 (−0.56 to 0.96) 5/5	$\chi^2(3) = 2.6, P = 0.45^a$ $\chi^2(1) = 0.5, P = 0.50^b$
MU head pref	9.34 (2.92)	9.92 (2.50)	10.12 (2.79)	11.85 (2.91)	$F(3, 77) = 1.5, P = 0.21, \eta^2 = 0.06$
MU head npref	12.55 (4.60)	12.22 (3.25)	14.48 (5.56)	14.05 (5.28)	$F(3, 77) = 1.5, P = 0.23, \eta^2 = 0.05$
MU pa shoul pref	15.28 (3.81)	16.36 (3.69)	15.75 (2.74)	18.60 (2.32)	$F(3, 77) = 3.8, P = 0.01, \eta^2 = 0.13$
MU pa shoul npref	18.50 (4.96)	18.19 (5.00)	18.80 (5.15)	20.96 (4.42)	E-PT > Term ^d , $t = 3.3, P = 0.008^e, \eta^2 = 0.12$
MU act shoul pref	15.92 (4.44)	17.40 (3.38)	18.68 (4.31)	19.48 (3.68)	$F(3, 77) = 0.85, P = 0.47, \eta^2 = 0.03$
MU act shoul npref	20.19 (6.80)	18.60 (3.65)	19.72 (5.46)	21.75 (3.63)	E-PT > Term ^d , $t = 2.7, P = 0.049^e, \eta^2 = 0.09$
MU act elb pref	10.01 (1.91)	10.05 (2.02)	10.16 (1.47)	12.29 (2.62)	$F(3, 77) = 0.70, P = 0.56, \eta^2 = 0.03$
MU act elb npref	11.38 (2.75)	10.83 (1.93)	11.16 (2.23)	12.27 (2.32)	$F(3, 77) = 5.1, P = 0.003, \eta^2 = 0.17$
MU act wr pref	7.78 (1.20)	7.91 (1.47)	8.15 (1.78)	9.65 (1.63)	E-PT > Term ^d , $t = 3.8, P = 0.002^e, \eta^2 = 0.16$
MU act wr npref	9.34 (2.83)	8.86 (1.78)	9.06 (1.89)	10.44 (2.50)	E-PT > M-PT ^d , $t = 3.3, P = 0.010^e, \eta^2 = 0.12$
MU act comp pref	11.24 (2.35)	11.79 (1.96)	12.33 (2.33)	13.81 (2.47)	$F(3, 77) = 1.1, P = 0.35, \eta^2 = 0.04$
MU act comp npref	13.64 (3.83)	12.76 (2.15)	13.31 (2.71)	14.82 (2.47)	E-PT > Term ^d , $t = 4.3, P < 0.001^e, \eta^2 = 0.20$
MU act ind pref	9.89 (1.96)	9.77 (1.84)	9.76 (1.27)	11.85 (2.29)	E-PT > M-PT ^d , $t = 3.6, P = 0.003^e, \eta^2 = 0.14$
MU act ind npref	11.74 (2.72)	11.41 (1.80)	11.21 (2.58)	13.00 (3.19)	$F(3, 77) = 1.2, P = 0.30, \eta^2 = 0.05$
					$F(3, 77) = 5.2, P = 0.003, \eta^2 = 0.17$
					E-PT > Term ^d , $t = 3.7, P = 0.002^e, \eta^2 = 0.15$
					$F(3, 77) = 1.1, P = 0.36, \eta^2 = 0.04$
					$F(3, 77) = 4.6, P = 0.005, \eta^2 = 0.15$
					E-PT > Term ^d , $t = 3.6, P = 0.003^e, \eta^2 = 0.14$
					E-PT > M-PT ^d , $t = 3.2, P = 0.013^e, \eta^2 = 0.12$
					E-PT > V-PT ^d , $t = 2.7, P = 0.048^e, \eta^2 = 0.09$
					$F(3, 77) = 1.4, P = 0.24, \eta^2 = 0.05$

For the lateralization indices, median, and [range] are shown on the first line and the number of subjects with right (R)/non-right (NR) preference on the second line. Non-right corresponds to those classed with left and non-evident preference. For the movement segmentation data, mean, and (SD) are presented. The statistics column includes the chi-square value (*df* in brackets) and the corresponding *P*-value for the lateralization indices. For the movement segmentation, the statistics column includes the *F*-ratio (*df* in brackets) with the corresponding *P*-value and partial eta square (η^2). In cases where a significant group effect was observed, the differing groups with the corresponding *t*-test value, *P*-value, and η^2 are also shown. *Abbreviations:* Term, term born; M-PT, moderately preterm; V-PT, very preterm; E-PT, extremely preterm; *N*, number of subjects; Lat, lateralization; MU, movement units; pa, passive; act, active; shoul, shoulder; elb, elbow; wr, wrist; comp, composite (active shoulder, elbow, and wrist); ind, index finger; pref, movement with the preferred side; non-pref, movement with the non-preferred side

^aKruskal–Wallis test on the four subgroups.

^bChi-square test on the term born versus the preterm group (pooled) testing the distribution of right v. non-right cases.

^cNot tested, as all cases but four had an index of +1 or −1.

^dBased on estimated marginal means evaluated at age = 7.9 years.

^eBonferroni corrected for multiple comparison.

3D Movement Registration and Analysis

For a comprehensive description of the movement registration, see Johansson et al. [2014]. Movements were recorded while performing a goal-directed, uni-manual, fine motor task requiring mid-line crossing (sequentially picking beads and threading them onto a thin rod situated at the contralateral side of the picking hand). The children were instructed to pick and thread as many beads as possible onto the rod, one at the time, during 30 seconds. The trial was repeated six times, three for each side, in a pairwise, randomized order. To classify the movement data according to hand preference (preferred or non-preferred), the outcomes from the test of hand laterality were used. If a child had a non-evident hand preference, a hand preference for the upper-limb movement registration was nonetheless ascribed based on the hand used most frequently for drawing or writing during the test of hand laterality.

Motion markers were affixed to the child's left and right shoulders, elbows, wrists, index fingers, and forehead, and the movements were recorded in 3D at a sampling frequency of 120 Hz using a six-camera optoelectronic registration system (ProReflex, Qualisys Inc., Gothenburg, Sweden). Simultaneous 2D video recordings were made to support the 3D movement data processing. During the analysis, marker omissions below 10 frames were automatically gap-filled by the system software, but the gap-fill was always visually inspected (and adjusted if needed) before acceptance. Larger gaps (10–20 frames) were checked in all three planes (X, Y, Z) and for acceleration and velocity profiles before acceptance.

The recorded data were smoothed using a second order 12 Hz Butterworth filter. Movement segmentation in terms of number of movement units (MUs) for each marker were extracted using an in-house MATLAB script (The Mathworks Inc., Boston, MA). A MU is a segmentation of the movement trajectory defined as an acceleration phase followed by a deceleration phase with an accumulated increase or decrease in velocity of at least 20 mm/s and an acceleration or deceleration exceeding 5 mm/s² [Von Hofsten, 1991].

During a pick-thread-pick cycle, movement for the markers of the shoulder, elbow, wrist, and index finger on the active (reaching) side were registered together with movement related to the passive shoulder and the forehead. Thus, when the preferred side was the active side, the passive shoulder is on the non-preferred side and vice versa. For each anatomical marker on the preferred and non-preferred side, the number of MUs was calculated as the “mean of means,” that is, first calculating the mean MU in relation to the number of pick-thread-pick cycles during the 30 s period, excluding data from unsuccessful cycles (dropping or picking multiple beads), and then calculating the mean MU across the three 30 s repetitions.

Diffusion Tensor Imaging (DTI)

DTI was performed in a 3T MRI scanners (Philips Medical Systems, Best, The Netherlands), using single-shot spin echo

EPI sequences with the following parameters: TR = shortest, TE = 70 ms, flip angle = 90 degrees, FOV = 224 × 224 mm, acquisition matrix = 112 × 112, # slices = 60 (contiguous), slice thickness = 2 mm, *b*-value = 1000 s/mm², # gradients = 32, SENSE factor = 2, and EPI factor = 55. One non-gradient volume was also sampled.

The images were processed in FSL (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT>), [Jenkinson et al., 2012] starting with converting the DTI images to NIFTI format and extracting the B₀-volume using *bet* [Smith, 2002]. The resulting B₀-images were visually scrutinized to ensure that each volume was appropriately extracted. Applying *eddy* [Andersson and Sotiropoulos, 2016], the diffusion weighted images were subjected to realignment and motion and eddy current correction. Quadratic terms were used for the spatial model of the eddy current induced field and the model of the diffusion gradients. The estimation was performed using a splined interpolation model; Jacobian modulation was used for the final resampling. Data were pre-filtered with a Gaussian filter with fwhm = 1 mm. All images were visually checked after the correction procedure and all samples passed the inspection. The DTI maps for fractional anisotropy (FA), mean diffusion (MD), axial diffusion (AD), and radial diffusion (RD) were subsequently generated by fitting diffusion tensors to the corrected data using *dtifit*. The FA represents the diffusional directionality and MD corresponds to the average, three-dimensional diffusion. AD, a.k.a. longitudinal or main diffusion, is the diffusion in the main diffusion direction and RD is the transverse diffusion, that is, the diffusion orthogonal to AD.

As the diffusional changes along white matter tracts in children born PT are not necessarily homogenous [Groeschel et al., 2014; Li et al., 2015; Travis et al., 2015], and because brain size and geometry depend on GA, particularly in the periventricular areas as children with lower GA have larger ventricles [Nosarti et al., 2002; Raybaud, 2016], the analysis of white matter was performed as an individual regions-of-interest (ROI) analysis. An additional important reason for using ROI analysis instead of whole-brain analysis was that the brain hemispheres, instead of being designated according to left/right, had to be categorized in relation to preferred/non-preferred side based on the side preference determined for the movement registration. The targeted areas were located in tracts assumed to be relevant for movement segmentation, but also areas that in previous studies have been demonstrated to be affected in children born PT [Li et al., 2015]. ROIs were drawn in the following regions (Fig. 1): corpus callosum (genu, truncus, and splenium), internal capsule (anterior and posterior), prefrontal cortex, optic radiation, superior and inferior longitudinal fasciculus, middle cerebellar peduncle, and the cerebral peduncle. The ROIs in the posterior internal capsule and the cerebral peduncle targeted the corticospinal tract. Outlining of the ROIs was performed in high-resolution T₂-images to which the diffusion images were registered using *FLIRT* in FSL. The outlining

Figure 1.

Regions-of-interest (ROI) in the brain. The ROIs on the images have been outlined in a drawing software to facilitate viewing of the images, and they correspond to the actual ROIs outlined in the analyzing software. ROI sizes were constant for all brains, and the outlining was adapted to the particular brain in order to target the area in question. A: Middle cerebellar peduncle, 79 mm²; B: cerebral peduncle, 32 mm²; C: inferior longitudinal

fascicle, 48 mm²; D: (i) genu of corpus callosum, 56 mm², (ii) anterior limb of the internal capsule, 38 mm², (iii) posterior limb of the internal capsule, 38 mm²; E: optic radiation, 48 mm²; F: (i) frontal white matter anterior, 56 mm², (ii) frontal white matter lateral 56 mm², (iii) splenium of corpus callosum, 56 mm²; G: truncus of corpus callosum, 96 mm²; H: superior longitudinal fascicle, 176 mm².

was performed by an operator specialized in DTI analysis (NL), and the outlined ROIs were subsequently copied to the DTI maps where FA, MD, RD, and AD for the specific regions were calculated. The outlining and calculations were performed in ImageJ (ImageJ 1.48, National Institutes of Health, USA, <http://rsb.info.nih.gov/ij>). The FA values of the designated areas on the left and right side are shown in Table I.

On 20% of the material (randomly selected in proportion to group sizes and using all outlined ROIs), the intra- and interrater reproducibility of drawing the ROIs was tested. Blinded to the results of the first outlining and to the group affiliation of the subject, a second operator (WH) outlined the same ROIs and the main operator performed a second outlining from scratch. WH was a medical intern trained for 6 months in outlining brain structures. Using FA as test parameter, the intra- and interrater correlations were $r = 0.89$ and $r = 0.87$, respectively ($P < 10^{-6}$ for both correlations), verifying the reproducibility of the ROI outlining.

Statistical Analysis

Group differences

Group differences on the lateralization indices between the four GA groups were tested using Kruskal–Wallis

tests. In addition, the distribution of the lateralization (right vs. non-right) was tested between term and PT born (pooling the three PT groups) using chi-square tests. The reason for pooling in the chi-square tests was that the number of cases of non-right was too few in each PT subgroup for comparing the four groups.

Outcomes for the movement data (MUs of the anatomical markers related to the forehead, passive shoulder, active shoulder, elbow, wrist, and index finger, and the composite measure of active shoulder–elbow–wrist) were tested for group differences using one-way ANCOVAs with chronological age as continuous covariate. Data from each side and marker were tested in separate models. In a similar manner, the side differences between the preferred and non-preferred side for each marker were also tested for between-group effects using one-way ANOVAs (not including age as covariate). Within-group side differences for the number of MUs were also tested for each marker using one sample *t*-tests.

Based on the definition of preferred/non-preferred side in the movement registration, the diffusion ROIs on each side were categorized accordingly in each participant, that is, if the preferred arm/hand was on the anatomical right side, the right hemisphere was considered to be located on the preferred side and the left hemisphere on the non-preferred side. The labeling of preferred/non-preferred hemisphere is

consequently not related to hemispheric dominance as such, it is just a tool to methodologically assign the hemispheres concordant with the side preference of the movement registration. FA, MD, RD, and AD in the ROIs were applied to a three-way MANCOVA with age as continuous covariate to test for group effects in each sidewise area after adjusting for the main effects of area and side. The diffusion measures in the ROIs in the corpus callosum were modeled in a similar manner (excluding side in the model). Side differences (preferred vs. non-preferred) were similarly modeled to test for between-group effects on the side differences of the diffusion. Additionally, the side differences for FA were tested for within-group effects in each area using one sample *t*-tests. The multivariate statistics *Pillai's trace* was used as statistics for the MANCOVAs.

Correlations

To investigate the connection between the microstructural alterations in the brain and the movement segmentation (MUs), FA from ROIs in the preferred and non-preferred hemisphere, respectively, were correlated (Pearson) with the number of MUs for each anatomical marker on each side (preferred and non-preferred). Thus, the correlations were performed both contra- and ipsilaterally. The relation between lateralization indices (hand, leg/foot, and total) and microstructure was examined by correlating (Spearman) the absolute value of the lateralization indices with the absolute value of the side difference of FA in the bilateral ROIs and with the callosal FA. The eye lateralization index was examined differently, as all subjects but four had an eye lateralization index of +1 or -1, making the absolute measure inappropriate for comparison. Instead, the four deviating children were assigned an index of +1 if the original index was positive and -1 if it was negative. Then, Mann-Whitney *U* tests were used to test if the side differences in FA in the targeted bilateral brain regions differed between the +1 and -1 group, and if the callosal FA differed between the groups.

If there was a significant correlation for FA on any of these tests, the correlation analyses were performed for MD, RD, and AD as well.

The statistical analyses were carried out in IBM SPSS 24.0 (IBM Corp., Armonk, NY) using $P \leq 0.05$ as threshold of significance (Bonferroni corrected for multiple comparisons). Partial eta square was used for describing effect sizes when appropriate, calculated as $SS_{\text{Effect}} / (SS_{\text{Effect}} + SS_{\text{Error}})$ where SS_{Effect} is the sum of squares for the effect in question and SS_{Error} is the sum of squares for the error.

RESULTS

Laterality Preferences and Movement Segmentation

There were no significant group effects with regard to the Kruskal-Wallis test of the lateralization indices, but the

chi-square tests showed a skewed distribution of the frequencies of hand lateralization with non-right handedness being more common in the pooled PT group (Table II).

Outcome for measures of movement segmentation (movement units [MUs]) during the pick-and-thread task revealed that, for movements with the preferred side, the children born E-PT had a significant increase in movement segmentation compared with the term born group, with the exception of the forehead (Table II). In addition, also for the preferred side, the children born E-PT had significantly more MUs than children born M-PT for the elbow, wrist, and the index finger, and compared with the V-PT group for MUs related to the index finger. Age had a significant negative effect on the number of MUs for all movement markers except two markers related to movement with the non-preferred side: the active shoulder and the composite (active shoulder-elbow-wrist) measure.

Regarding between-group effects for the side differences, there was no significant effect for any marker ($P > 0.18$).

Within-group effects on side differences were demonstrated in several instances: the term born children had significant side differences in terms of number of MUs for all markers ($P < 0.001$). Likewise, for the M-PT group, side differences were observed for the markers of the forehead ($P = 0.001$), wrist ($P = 0.015$), composite measure ($P = 0.047$), and the index finger ($P = 0.003$). The children born V-PT only showed side differences for the forehead marker ($P = 0.011$) and the passive shoulder marker ($P = 0.035$), and the children born E-PT showed no significant side differences. In all cases where there was a significant side difference, the average number of MUs was higher when the pick-and-thread movement was performed with the non-preferred side. Thus, although within-group effects were demonstrated for the side differences for certain markers and groups, side differences did not show between-group effects for any marker.

Diffusion Data

In the MANCOVA model for the bilateral brain areas, all included terms were significant (age, $P = 0.03$; area, $P < 0.001$; side, $P < 0.001$; and area $\times$ side $\times$ group, $P = 0.02$). Three side specific areas showed significant multivariate group effects for the cross term: the anterior limb of the internal capsule (ALIC) on the preferred side ($P = 0.043$), the optic radiation on the non-preferred side ($P = 0.048$), and the cerebral peduncle on the non-preferred side ($P < 0.001$). Individual F-tests for each diffusion measure showed that for the ALIC on the preferred side, there was a significant effect for FA ($F(3, 1403) = 2.77$, $P = 0.041$) and AD ($F(3, 1403) = 2.75$, $P = 0.042$). The optic radiation on the non-preferred side only showed an effect for RD ($F(3, 1403) = 2.65$, $P = 0.048$). For the cerebral peduncle on the preferred side, there were significant effects for FA ($F(3, 1403) = 2.78$, $P = 0.040$), MD ($F(3,$

1403) = 4.30, $P = 0.005$, and RD ($F(3, 1403) = 4.80$, $P = 0.002$). The corresponding model for the corpus callosum showed significant multivariate effects for the terms area and area $\times$ group (both $P < 0.001$), but not for age ($P = 0.88$). Multivariate group effects were observed for the splenium ($P < 0.001$) and the truncal part ($P = 0.047$). The F-tests showed that for the splenium, there were significant effects for FA ($F(3, 233) = 3.06$, $P = 0.029$), MD ($F(3, 233) = 9.76$, $P < 0.001$), and RD ($F(3, 233) = 6.67$, $P < 0.001$); and for the truncus, there were significant effects for FA ($F(3, 233) = 3.09$, $P = 0.028$) and RD ($F(3, 233) = 2.68$, $P = 0.048$). The estimated group means for all diffusion measures in the areas that showed significant multivariate effects, together with the pairwise comparisons for the diffusion measures that show significant differences between groups, are shown in Table III.

For the side differences, the MANCOVA model was not significant for any of the included terms (age, $P = 0.33$; area, $P = 0.09$; and area $\times$ group, $P = 0.98$); hence, no further results of the between-group effect on the side differences of the diffusion measures in specific areas are presented.

Concerning within-group effects, significant side differences (preferred vs. non-preferred side) of FA were present in the following areas in the term born group: ALIC ($\Delta = -0.039$, $P = 0.044$), PLIC ($\Delta = -0.033$, $P < 0.001$), inferior longitudinal fascicle (ILF) ($\Delta = -0.033$, $P = 0.003$), and the cerebral peduncle ($\Delta = -0.035$, $P < 0.001$). For the children born M-PT, significant side differences were observed for FA in the PLIC ($\Delta = -0.030$, $P = 0.037$), the superior longitudinal fascicle (SLF) ($\Delta = -0.022$, $P = 0.032$), and the middle cerebellar peduncle ($\Delta = -0.041$, $P = 0.040$). For the V-PT and E-PT groups, no significant side differences were observed. Thus, similar to the results for the movement segmentation, the groups with higher GA demonstrate significant within-group side differences in FA in certain areas, but between-group effects on side differences did not reach statistical significance for any area.

Correlations Between Movement Outcomes and Diffusion Measures

Correlations between FA and movement segmentation in terms of the number of MUs were observed in the ALIC, PLIC, ILF, SLF, and the cerebral peduncle. No correlations were observed for corpus callosum. The results for the ALIC, PLIC, and the cerebral peduncle are shown in Table IV. Notably, FA in the ALIC and the PLIC show *positive* correlations with the number of MUs of multiple movement markers, both in a contra- (i.e., diffusion on the non-preferred side vs. movement data on the preferred side or vice versa) and ipsilateral (i.e., diffusion vs. movement data on the same side) fashion, whereas in the cerebral peduncle, the corresponding correlations are *negative* (Fig. 2). The ILF on the preferred side showed the following correlations between FA (RD where applicable) and

the number of MUs for the movement markers: the forehead (movement with the preferred side), $r = 0.22$, $P = 0.05$; passive shoulder (movement with the preferred side), $r = 0.29$, $P = 0.009$ (also RD, $r = -0.24$, $P = 0.03$); active shoulder (movement with the preferred side), $r = 0.27$, $P = 0.01$; and the composite measure (movement with the preferred side), $r = 0.26$, $P = 0.02$. The SLF on the preferred side showed correlations between FA ($r = -0.27$, $P = 0.02$) and RD ($r = 0.29$, $P = 0.008$) and the number of MUs for the forehead (movement with the non-preferred side), and the SLF on the non-preferred side showed a correlation between FA and the number of MUs for the active shoulder (movement with the non-preferred side) ($r = -0.23$, $P = 0.042$).

Correlations Between Lateralization Indices and Diffusion Measures

There were no correlations between the absolute value of the lateralization indices (hand, foot, and total) and the absolute side differences of FA in any brain region. The side differences of FA had no effect on the eye lateralization index either. The absolute lateralization index of handedness did not correlate with FA in the callosal areas, but the absolute lateralization index of the foot correlated with the diffusion in the truncus corpus callosum: FA ($r = -0.25$, $P = 0.02$), MD ($r = 0.24$, $P = 0.03$), and RD ($r = 0.27$, $P = 0.02$). Additionally, the absolute total lateralization index correlated with the diffusion in the truncus corpus callosum: FA ($r = -0.26$, $P = 0.02$), MD ($r = 0.24$, $P = 0.03$), and RD ($r = 0.27$, $P = 0.02$). Participants with a negative eye lateralization index ($N = 30$) had higher FA (median 0.72 vs. 0.66, $U = 510$, $z = -2.6$, $P = 0.009$) and lower MD (median 824 vs. 865×10^{-6} mm²/s, $U = 516$, $z = -2.5$, $P = 0.011$) and RD (median 406 v. 478×10^{-6} mm²/s, $U = 507$, $z = -2.6$, $P = 0.009$) in truncus corpus callosum than those with a positive index ($N = 52$).

Post-Hoc Tests of Ventricular Size and Evans Index

Based on the differences between groups regarding ventricular width and Evans index, see Table I, we correlated these measures with FA of the ALIC, PLIC, and the corpus callosum to examine if ventricular expansion could be an explanatory factor for the FA values of the adjacent white matter structures, in a manner similar to that in normal pressure hydrocephalus [Hattingen et al., 2010; Hattori et al., 2011]. A positive correlation was identified between FA in the ALIC on the preferred side and the ventricular width ($r = 0.23$, $P = 0.04$), and also between FA in the PLIC on the preferred side and the Evans index ($r = 0.24$, $P = 0.03$). No correlations were observed for FA in either callosal area.

TABLE III. Diffusion measures in target areas with a significant multivariate effect on group

	Diffusion measure	Term N = 41	M-PT N = 18	V-PT N = 13	E-PT N = 10	Statistics
ALIC pref	FA	0.50 (0.09)	0.52 (0.07)	0.49 (0.09)	0.55 (0.09)	E-PT > Term ^a , $t = 2.3$, $P = 0.024^b$, $\eta^2 = 0.007$; E-PT > V-PT ^a , $t = 2.4$, $P = 0.016^b$, $\eta^2 = 0.008$
	MD $\times 10^{-6}$ (mm ² /s)	759 (70)	790 (106)	762 (66)	743 (82)	E-PT < M-PT ^a , $t = -2.0$, $P = 0.049^b$, $\eta^2 = 0.005$
	RD $\times 10^{-6}$ (mm ² /s)	523 (86)	539 (106)	534 (78)	480 (94)	E-PT < M-PT ^a , $t = -2.0$, $P = 0.044^b$, $\eta^2 = 0.006$
	AD $\times 10^{-6}$ (mm ² /s)	1228 (113)	1294 (120)	1220 (123)	1264 (129)	M-PT > V-PT ^a , $t = 2.1$, $P = 0.034^b$, $\eta^2 = 0.006$; M-PT > Term ^a , $t = 2.4$, $P = 0.015^b$, $\eta^2 = 0.008$
OR npref	FA	0.55 (0.04)	0.56 (0.06)	0.55 (0.06)	0.50 (0.04)	E-PT < M-PT ^a , $t = -2.0$, $P = 0.048^b$, $\eta^2 = 0.005$
	MD $\times 10^{-6}$ (mm ² /s)	856 (48)	846 (58)	874 (58)	892 (46)	E-PT > M-PT ^a , $t = 2.1$, $P = 0.041^b$, $\eta^2 = 0.005$
	RD $\times 10^{-6}$ (mm ² /s)	565 (48)	551 (64)	573 (83)	622 (37)	E-PT > M-PT ^a , $t = 2.2$, $P = 0.032^b$, $\eta^2 = 0.007$; E-PT > Term ^a , $t = 2.4$, $P = 0.017^b$, $\eta^2 = 0.008$
	AD $\times 10^{-6}$ (mm ² /s)	1438 (85)	1435 (107)	1477 (75)	1433 (94)	–
CP npref	FA	0.75 (0.07)	0.77 (0.08)	0.73 (0.06)	0.72 (0.06)	E-PT < M-PT ^a , $t = -2.0$, $P = 0.047^b$, $\eta^2 = 0.005$
	MD $\times 10^{-6}$ (mm ² /s)	816 (87)	799 (82)	839 (80)	880 (99)	E-PT > M-PT ^a , $t = 3.4$, $P = 0.001^b$, $\eta^2 = 0.016$; E-PT > Term ^a , $t = 3.0$, $P = 0.003^b$, $\eta^2 = 0.012$
	RD $\times 10^{-6}$ (mm ² /s)	379 (99)	348 (113)	409 (92)	452 (114)	E-PT > M-PT ^a , $t = 3.5$, $P = 0.001^b$, $\eta^2 = 0.017$; E-PT > Term ^a , $t = 2.7$, $P = 0.007^b$, $\eta^2 = 0.011$; V-PT > M-PT ^a , $t = 2.2$, $P = 0.027^b$, $\eta^2 = 0.007$
	AD $\times 10^{-6}$ (mm ² /s)	1690 (125)	1699 (86)	1698 (107)	1737 (131)	–
CC trunc	FA	0.68 (0.09)	0.71 (0.09)	0.63 (0.10)	0.63 (0.10)	E-PT < M-PT ^a , $t = -2.3$, $P = 0.021^b$, $\eta^2 = 0.023$; V-PT < M-PT ^a , $t = -2.5$, $P = 0.011^b$, $\eta^2 = 0.028$
	MD $\times 10^{-6}$ (mm ² /s)	855 (107)	827 (73)	876 (80)	910 (97)	E-PT > M-PT ^a , $t = 2.3$, $P = 0.022^b$, $\eta^2 = 0.022$
	RD $\times 10^{-6}$ (mm ² /s)	461 (141)	412 (109)	512 (136)	533 (144)	E-PT > M-PT ^a , $t = 2.4$, $P = 0.016^b$, $\eta^2 = 0.025$; V-PT > M-PT ^a , $t = 2.2$, $P = 0.028^b$, $\eta^2 = 0.021$
	AD $\times 10^{-6}$ (mm ² /s)	1643 (113)	1655 (93)	1604 (60)	1666 (66)	–
CC splen	FA	0.81 (0.08)	0.81 (0.10)	0.79 (0.07)	0.72 (0.12)	E-PT < M-PT ^a , $t = -2.4$, $P = 0.015^b$, $\eta^2 = 0.025$; E-PT < Term ^a , $t = -3.0$, $P = 0.003^b$, $\eta^2 = 0.036$
	MD $\times 10^{-6}$ (mm ² /s)	778 (75)	776 (83)	789 (58)	945 (131)	E-PT > V-PT ^a , $t = 4.1$, $P < 0.001^b$, $\eta^2 = 0.06$; E-PT > M-PT ^a , $t = 4.7$, $P < 0.001^b$, $\eta^2 = 0.087$; E-PT > Term ^a , $t = 5.2$, $P < 0.001^b$, $\eta^2 = 0.10$
	RD $\times 10^{-6}$ (mm ² /s)	292 (108)	294 (131)	325 (90)	484 (161)	E-PT > V-PT ^a , $t = 3.0$, $P = 0.003^b$, $\eta^2 = 0.037$; E-PT > M-PT ^a , $t = 3.8$, $P < 0.001^b$, $\eta^2 = 0.059$; E-PT > Term ^a , $t = 4.4$, $P < 0.001^b$, $\eta^2 = 0.076$
	AD $\times 10^{-6}$ (mm ² /s)	1750 (186)	1739 (136)	1717 (134)	1873 (196)	E-PT > V-PT ^a , $t = 2.3$, $P = 0.022^b$, $\eta^2 = 0.022$; E-PT > M-PT ^a , $t = 2.1$, $P = 0.036^b$, $\eta^2 = 0.019$; E-PT > Term ^a , $t = 2.2$, $P = 0.030^b$, $\eta^2 = 0.020$

Numbers represent mean and (SD). The statistics column shows the groups that differ for each measure and the corresponding t -value (t), P -value (P), and partial eta square (η^2). *Abbreviations:* Term, term born; M-PT, moderately preterm; V-PT, very preterm; E-PT, extremely preterm; N, number of subjects; pref, preferred side; npref, non-preferred side; ALIC, anterior limb of the internal capsule; OR, optic radiation; CP, cerebral peduncle; CC trunc, truncus of corpus callosum; CC splen, splenium of corpus callosum; FA, fractional anisotropy; MD, mean diffusion; RD, radial diffusion; AD, axial diffusion.

^aBased on estimated marginal means evaluated at age = 7.9 years.

^bBonferroni corrected for multiple comparison.

TABLE IV. Correlations between movement segmentation and diffusion measures in the ALIC, PLIC, and the cerebral peduncle

Marker	Hemi. of diff. meas.	ALIC				PLIC				CP			
		FA	MD	RD	AD	FA	MD	RD	AD	FA	MD	RD	AD
Forehead pref	ns	-	-	-	-	ns	-	-	-	ns	-	-	-
	0.23 ($P = 0.04$)	ns	ns	-	-	ns	-	-	-	ns	-	-	-
Forehead npref	ns	-	-	-	-	ns	-	-	-	-0.24 ($P = 0.03$)	ns	ns	ns
	ns	-	-	-	-	ns	-	-	-	ns	-	-	-
Pa shoul pref	ns	-	-	-	-	0.32 ($P = 0.003$)	ns	-0.29 ($P = 0.009$)	ns	-0.23 ($P = 0.04$)	0.27 ($P = 0.02$)	0.27 ($P = 0.02$)	ns
	0.24 ($P = 0.03$)	ns	ns	-0.32 ($P = 0.003$)	-0.23 ($P = 0.04$)	0.33 ($P = 0.002$)	-0.23 ($P = 0.04$)	-0.32 ($P = 0.003$)	ns	ns	-	-	-
Pa shoul npref	ns	-	-	-	-	ns	-	-	-	-0.24 ($P = 0.03$)	0.22 ($P = 0.04$)	0.24 ($P = 0.03$)	ns
	ns	-	-	-	-	ns	-	-	-	-0.24 ($P = 0.03$)	ns	0.23 ($P = 0.04$)	ns
Act shoul pref	ns	-	-	-	-	0.23 ($P = 0.04$)	ns	ns	ns	-0.25 ($P = 0.03$)	0.34 ($P = 0.002$)	0.29 ($P = 0.008$)	0.28 ($P = 0.01$)
	0.25 ($P = 0.03$)	ns	ns	ns	0.26 ($P = 0.02$)	0.23 ($P = 0.04$)	ns	-0.23 ($P = 0.04$)	ns	-0.23 ($P = 0.04$)	0.30 ($P = 0.006$)	0.24 ($P = 0.03$)	0.26 ($P = 0.02$)
Act shoul npref	ns	-	-	-	-	0.25 ($P = 0.02$)	ns	ns	0.24 ($P = 0.03$)	-0.30 ($P = 0.007$)	0.23 ($P = 0.04$)	0.27 ($P = 0.02$)	ns
	0.28 ($P = 0.01$)	ns	ns	-0.24 ($P = 0.03$)	ns	0.25 ($P = 0.02$)	ns	-0.24 ($P = 0.03$)	ns	ns	-	-	-
Act elb pref	ns	-	-	-	-	0.24 ($P = 0.03$)	ns	-0.23 ($P = 0.04$)	ns	-0.26 ($P = 0.02$)	0.34 ($P = 0.002$)	0.32 ($P = 0.004$)	0.24 ($P = 0.03$)
	ns	-	-	-	-	ns	-	-	-	ns	-	-	-
Act elb npref	ns	-	-	-	-	ns	-	-	-	-0.22 ($P = 0.04$)	ns	ns	ns
	ns	-	-	-	-	ns	-	-	-	ns	-	-	-
Act wr pref	ns	-	-	-	-	0.33 ($P = 0.002$)	ns	-0.27 ($P = 0.01$)	ns	-0.23 ($P = 0.04$)	0.26 ($P = 0.02$)	0.25 ($P = 0.02$)	ns
	ns	-	-	-	-	ns	-	-	-	ns	-	-	-
Act wr npref	ns	-	-	-	-	0.33 ($P = 0.002$)	ns	-0.25 ($P = 0.02$)	ns	ns	-	-	-
	ns	-	-	-	-	ns	-	-	-	ns	-	-	-
Act comp pref	ns	-	-	-	-	0.28 ($P = 0.01$)	ns	-0.22 ($P = 0.05$)	ns	-0.23 ($P = 0.03$)	0.35 ($P = 0.001$)	0.32 ($P = 0.004$)	0.27 ($P = 0.01$)
	0.22 ($P = 0.04$)	ns	ns	ns	ns	0.25 ($P = 0.03$)	ns	-0.22 ($P = 0.05$)	ns	-0.23 ($P = 0.03$)	0.27 ($P = 0.01$)	0.23 ($P = 0.04$)	0.23 ($P = 0.04$)
Act comp npref	0.23 ($P = 0.04$)	ns	ns	ns	0.23 ($P = 0.03$)	0.31 ($P = 0.005$)	ns	-0.22 ($P = 0.05$)	0.23 ($P = 0.04$)	-0.27 ($P = 0.02$)	ns	0.23 ($P = 0.04$)	ns
	0.22 ($P = 0.04$)	ns	ns	ns	ns	0.23 ($P = 0.04$)	ns	-0.23 ($P = 0.04$)	ns	ns	-	-	-
Act ind pref	ns	-	-	-	-	0.34 ($P = 0.002$)	ns	-0.27 ($P = 0.02$)	ns	-0.23 ($P = 0.04$)	0.23 ($P = 0.04$)	0.24 ($P = 0.03$)	ns
	ns	-	-	-	-	ns	-	-	-	ns	-	-	-
Act ind npref	ns	-	-	-	-	0.30 ($P = 0.006$)	ns	ns	0.25 ($P = 0.03$)	-0.27 ($P = 0.02$)	ns	0.24 ($P = 0.03$)	ns
	ns	-	-	-	-	ns	-	-	-	ns	-	-	-

Both contralateral (diffusion in the preferred hemisphere vs. segmentation on the non-preferred side or vice versa) and ipsilateral (diffusion vs. segmentation on the same side) are displayed. The rows contain the movement segmentation markers when moving the respective side (pref, preferred side; npref, non-preferred side) and the columns contain the diffusion metrics for the brain areas. The cells show the correlation coefficient (with the P -value in brackets) between the MUs of the marker in question and the diffusion measures in the preferred (pref) and the non-preferred (npref) hemisphere in the designated brain area. Non-significant correlations are expressed as "ns" and untested correlations (i.e., the correlations for FA were non-significant) are denoted with a dash (-). *Abbreviations:* ALIC, anterior limb of the internal capsule; PLIC, posterior limb of the internal capsule; CP, cerebral peduncle; FA, fractional anisotropy; MD, mean diffusion; RD, radial diffusion; Hemi., hemisphere; diff., diffusion; meas., measure; pa, passive; act, active; shoul, shoulder; elb, elbow; wr, wrist; comp, composite (shoulder, elbow, wrist); ind, index finger.

Figure 2.

Scatter plot of the number of movement units versus fractional anisotropy. Data are from all participants and apply to the composite measure (shoulder, elbow, and wrist) when moving the preferred side (y-axis) and the cerebral peduncle (corticospinal tract) on the non-preferred side (x-axis). MU, movement units; FA, fractional anisotropy; CST, corticospinal tract.

DISCUSSION

In this study, we have demonstrated that children born extremely PT (E-PT) have altered diffusivity in brain areas important for sensorimotor function. Notably, the fractional anisotropy (FA) in children born E-PT deviates from their term born counterparts in different manners in different areas: FA is increased in the anterior limb of the anterior capsule (ALIC) on the preferred side, but decreased in the cerebral peduncle (CP) on the non-preferred side. Furthermore, FA in these regions correlates with movement segmentation in a corresponding manner, suggesting that the altered microstructure in these areas in children born E-PT play an important role for their impeded upper-limb spatiotemporal movement organization during goal-directed activities.

The outcome from the movement registration shows that the poorer performance of the E-PT group primarily transpired on the preferred side (Table II). Notably, for most movement markers, the other PT groups (V-PT and M-PT) showed similar movement segmentation in terms of numbers of movement units (MUs) on the preferred side as the term born children. This finding emphasizes the increased risk for children born E-PT to develop poor motor function, supporting other findings [Goyen and Lui, 2009; Goyen et al., 2011], but it also suggests that extra-uterine development after the second trimester is not necessarily associated with less efficient movement execution *per se*. Furthermore, the observation highlights the benefits

of subgrouping based on GA within children born PT. The last trimester is a process of maturation and growth, but it also involves phases of development, particularly in its early stage. Thus, an extremely PT birth intervenes with development phases that cannot be extrauterinely completed to the same degree. Treating children born PT as merely a homogenous group with varying GA might unintentionally discount these intra/extrauterine developmental aspects of different GAs, possibly overemphasizing some infirmities for children that are born in the higher range of GAs considered as PT, and underrating them for those born in the lower range.

On the non-preferred side, the E-PT group also had increased movement segmentation compared with the term born group, but the larger variation in the number of MUs for each marker masks any statistical differences.

Movement Segmentation

The marker on the forehead and passive shoulder (the shoulder on the non-preferred side while moving the arm on the preferred side and vice versa) served the purpose of assessing the child's ability to stabilize his/her head and trunk during the movement. Head movements are related to the need for adjustments of the head to get appropriate visual input. Improper eye coordination in relation to activities of the extremities and the requirement of visual feedback will render in compensatory modifications of the position of the head, which in turn also can

affect the position of the trunk. Furthermore, the smoothness of the movement with the active hand depends on sensory feedback from joints and muscles and the integration of this information with visual feedback in order to give adequate input to the motor system for adjustments and planning. The E-PT group only displayed significantly more movement segmentation than the children born at term for the passive shoulder marker while performing the pick-and-thread task with the preferred hand (Table II); however, the children born E-PT underperformed regarding the forehead marker as well, although not significantly so. Thus, the results suggest that the children born E-PT performed more compensatory movements with the trunk and, to a lesser degree, head compared with peers born at term, particularly when acting with the preferred hand. There could be several reasons for this; the most obvious one being inadequate proprioception, or insufficient integration of proprioception into the high-level systems of motor control, resulting in compensatory positioning of the trunk and head to increase visual monitoring during the task performance. Such deficits could also be amplified by improper coordination between eye muscles and neck/head muscles. Another possibility is that the active arm movement caused inter-limb coupling to a higher degree in the E-PT group; that is, that the motor system in these children is less able to tune the activation of passive upper-body muscles when the active movement exerts recoupling momentum on the rest of the body. Additionally, in contrast to the term born group, the E-PT group showed no significant within-group side difference in terms of MUs of the forehead and passive shoulder markers. This finding implies a more complete specialization for movements with the preferred side in the term born group, and that this specialization includes stability measures not directly related to the movement of the preferred arm.

The number of MUs related to markers on the active side showed that the E-PT group underperformed relative to the term born group on the preferred side, and notably, differences were also present compared with the other PT groups for the more distal joints (Table II). No between-group differences were observed for the non-preferred side. A likely reason for these observations is differences in the level of specialization. It has been demonstrated that children born PT, especially those born in the lower GA range, are less side specific in terms of hemispheric dominance [Flamand et al., 2012], possibly due to limitations in brain plasticity and a less refined interaction between the hemispheres [Pitcher et al., 2012a,b]. The increased frequency of non-right handedness in the PT group and the almost significant group effect on hand lateralization, with the children born E-PT displaying less evident right-hand preference (Table II), support this notion. Thus, it is plausible that developmental disturbance of specialization not only increases the rate of non-right handedness, but also causes the dominant

hemisphere to become less specialized. The fact that significant differences in terms of the number of MUs were observed between the children born E-PT and the other PT groups (V-PT, M-PT) for the index finger on the preferred side further supports this hypothesis, as specialization is more pronounced for movements of the distal joints. The same pattern arises for the side differences: there is no between-group effect for side differences, but the term born children displayed significant within-group side differences in terms of MUs for the distal joints, whereas the V-PT and E-PT group did not.

Lateralization

Weaker lateralization and a higher proportion of non-right preference have been demonstrated in children born PT [Ashton, 1982; Ross et al., 1992]. However, our results suggest that this phenomenon mainly applies to manual activity (Table II). This is possibly related to the increased cortical representation of the hands compared with the feet, that is, proper gestational specialization development of the dominant hemisphere is more important for the cortical organization of the hand representation compared with the relatively crudely organized representation of the leg and foot. Similarly, no group differences were observed for the laterality index of the eyes. Still the E-PT group had a 1:1 distribution between right and non-right, whereas the term born group had approximately 2:1. Further studies are required to determine into which realms—beyond hands—that the tilted distribution of lateralization in children born PT extend.

Diffusion Alterations

The altered diffusion in the cerebral peduncle in the non-preferred hemisphere in the children born E-PT could be interpreted as an expression of their less evident hemispheric dominance. This ROI targets the corticospinal tract, primarily transmitting motor signaling to the preferred side. Thus, in a contralateral manner, this finding is in keeping with the group differences found for the movement performance. The alterations include significantly reduced FA for the E-PT group compared with the M-PT group, and significant increases in MD and RD for the E-PT group compared with the term born and M-PT groups (Table III). Findings suggest an impaired myelination of this tract, resulting in less accurate transmission to the downstream muscles and decreased smoothness of the movement, further supported by the correlation between the number of MUs of the composite measure on the preferred side and the FA, MD, RD, and AD of the cerebral peduncle on the non-preferred side (Table IV and Fig. 2). Additionally, we observed several correlations between the diffusion measures in the cerebral peduncle on the preferred side and the number of MUs for several markers on both the preferred and the non-preferred side. Thus,

although we did not find any group differences in the cerebral peduncle on the preferred side, possibly due to larger variation of the diffusion measures, these correlations still indicate that the changes in microstructure in this structure play an important role at the level of movement segmentation.

In contrast to the cerebral peduncle, we found significant positive correlations between FA in the PLIC and the composite MU measure. The corresponding correlations for RD were negative. The correlations applied both ipsi- and contralaterally and for both the preferred and non-preferred side. Additionally, for the individual markers, there are similar correlations for FA and RD in the PLIC on the preferred side. As this ROI also targets the corticospinal tract, similar to the ROI in the cerebral peduncle, associations between FA and movement segmentation appear to vary along the corticospinal tract. Notably, the correlations between the number of MUs and the diffusion measures in the PLIC are more similar to the ALIC than the cerebral peduncle, indicating that this might be related to the level in the brain. Interestingly, level-dependent differences of FA in the corticospinal tract between children born at term and PT have been reported previously [Groeschel et al., 2014; Travis et al., 2015], although, in our study, no group effect was observed for the diffusion measures in the PLIC. Nonetheless, in support of our findings, diffusion alterations in the corticospinal tract have been demonstrated to correlate with various measures of motor function in both young children and late adolescents born PT [De Kieviet et al., 2014; Eikenes et al., 2011; Sripada et al., 2015].

The children born E-PT exhibited significantly increased FA in the ALIC on the preferred side compared with the term born and V-PT groups. The difference seems to arise from decreased RD and increased AD, although the pattern is not as straightforward as in the cerebral peduncle. Furthermore, similarly to the PLIC, increasing FA in the ALIC was associated with worse performance in terms of number of MUs for the composite measure (Table IV). The ALIC contains the frontopontine tract and the anterior thalamic radiation. These fibers pass to and from the frontal cortex and the basal ganglia, thalamus, and the brain stem. These circuits are involved in high-order control of movements, including planning, coordination, and surveillance. Increased FA in the ALIC, or nearby areas, has previously been identified in children born PT [Allin et al., 2011; Groeschel et al., 2014], and decreased MD in the ALIC has been found in adults with developmental coordination disorder [Williams et al., 2017]. The mechanism behind this increase in FA is unknown. The positive correlation between FA in the ALIC on the preferred side and ventricular size indicates that tissue compression by enlarged ventricles might play a role, similar to the case in normal pressure hydrocephalus [Hattingen et al., 2010; Hattori et al., 2011]; however, none of the children born PT in this study was actually hydrocephalic. The similar

correlation between Evans index and FA in the PLIC supports this notion, possibly explaining why the diffusion measures in this area have an inverse relation to the MUs from the movement measurements compared with the cerebral peduncle. Another possibility is that the increased FA in the ALIC is a compensatory mechanism [Allin et al., 2011] in relation to the suggested impaired myelination observed in the corticospinal tract, that is, that tracts involved in higher-order or indirect circuits related to movement execution are “enhanced” to compensate for the less intact direct pathways. The differences might also be attributed to differences in terms of developmental stages of various parts of the brain [Barnea-Goraly et al., 2005; Giedd et al., 1999], or perinatal brain lesions [Nosarti et al., 2008]. An example of the early developmental aspects, returning to the cerebral peduncle, is that close to birth, FA is increased in this structure in children born V-PT, whereas FA is decreased in several other white matter structures [Rose et al., 2008]. Reduced number of crossing-fiber can also increase FA [Groeschel et al., 2014; Hoeft et al., 2007], and so can deficits in the axonal structure or branching [Beaulieu, 2002]. A last note on the ALIC, PLIC, and the cerebral peduncle is that these structures demonstrate side differences of the diffusion measures in the term born group, but not in the E-PT and V-PT group; an observation that further supports the notion of superior specialization in the dominant hemisphere in the term born children.

Reduced FA in the corpus callosum in individuals born PT has been repeatedly reported [Andrews et al., 2010; Eikenes et al., 2011; Mullen et al., 2011; Vangberg et al., 2006]. The feature is observed already at birth and infancy [Rose et al., 2008; Thompson et al., 2012], and it seems particularly prominent in the splenium. This fits with our results, where the E-PT group differs from all other groups in almost all diffusion measures for the splenium (Table III). In the truncal part, the differences for FA and RD in the E-PT group only apply in relation to the M-PT group, but they apply for the V-PT group as well and the overall picture is the same. The reason for the finding of no differences in the genu might be that the differences are found more laterally in this structure (our ROI is centered, see Fig. 1) and/or that they are more pronounced on other levels.

Despite the severe alterations in the corpus callosum, there were no correlations between the diffusion measures in this structure and movement segmentation. This is possibly due to the fact that the movement task did not require an active collaboration between the left and right side. Instead, we observed that higher FA values in the truncal part were associated with less absolute lateralization for the lower extremities and the total measure. This might indicate that less specialization of the dominant hemisphere is to some degree compensated by denser interhemispheric connections, or that a well-developed specialization on one side actually requires fewer

interhemispheric connections with the other side. Possibly, it can also relate to differences in myelination as indicated by the corresponding correlations for RD. The differences in trunca FA between those children with a positive and a negative eye lateralization index give further support for the significance of the development of the corpus callosum for functional lateralization, but further studies are required to understand why a left-sided eye preference is associated with higher FA.

Correlations with the number of MUs for a few of the markers were also observed for FA in the ILF and the SLF, but none of these structures showed differences at the group level. These structures have previously been reported as having reduced FA in a meta-study on children born PT [Li et al., 2015]. More interestingly, we found altered diffusion measures in the optic radiation in children born E-PT, although the difference in FA only applied compared with the M-PT group. Similar results have been demonstrated in children with low birth weight [Sripada et al., 2015]. Whilst no correlations with movement segmentation were observed for the diffusion measures in the optic radiation, this observation might still be important concerning the integration of visual input to the sensorimotor system in the brain.

The interpretation of altered FA in the various areas in terms of microstructural alterations is indeed complex, particularly in cross-fiber areas where the main axis of diffusivity varies significantly, clouding the usefulness of AD and RD to interpret changes in FA [Wheeler-Kingshott and Cercignani, 2009]. Groeschel et al. have demonstrated that increased FA in children born PT is primarily confined to areas with high rates of crossing-fibers, where the loss of one fiber direction increases AD and subsequently FA [Groeschel et al., 2014]. Thus, the increased FA at more cranial levels of, for instance, the craniospinal tract might be an “illusion” caused by an actual “low-FA” fiber bundle crossing other intact bundles. They also suggest partial volume effects from neighboring cerebrospinal fluid as a possible explanation for the observed reduced callosal FA, possibly related to thinning of this structure in children born PT, especially in those with cerebral pathology [Groeschel et al., 2014]. These explanations are important considerations when interpreting diffusion parameters in the brains of children born PT and highlight the need for future studies to better comprehend the diffusivity changes related to a PT birth.

Limitations

The study is limited by the relatively few individuals in the subgroups of the PT group. The advantage of this subdivision, however, was that we could show that the children born E-PT deviated on several measures concerning movement segmentation and diffusion metrics. We were also able to show that children born at moderate GA basically did not differ at all from the children born at term.

It is well recognized that children born PT are at higher risk for acquiring cerebral injuries during the perinatal

period, as indicated in Table I, and that such injuries might influence behavior later in life [Deng, 2010; Linsell et al., 2015]. Unfortunately, due to small sample sizes in the V-PT and E-PT groups, we had to refrain from examining this perspective. However, as outcome differences primarily relate to the E-PT group, and the E-PT and V-PT groups had more or less equal ratios of cerebral pathology, such influences are not directly implied, but nevertheless cannot be excluded. Larger sample sizes are required to verify this effect, especially as various pathologies and their localization possibly have different impact on neurodevelopmental outcome.

The ROI analysis does not take entire tracts into consideration; however, tract based analysis can be deceitful in developing brains [Groeschel et al., 2014]. ROI analysis has the advantage of eliminating the risk for misalignment during the normalization process associated with tract-based analysis. This aspect is particularly important as the hemispheres needed to be categorized based on preferred/non-preferred side, not left/right; a fact that complicates normalization and group averaging related to whole-brain analysis. Still, partial volume effects from adjacent structures can affect measurements [Vos et al., 2011]. We tried to minimize this effect by using constant-size ROIs lying entirely within the designated areas. Furthermore, and as pointed out by others [Li et al., 2015], DTI is a technique sensitive to various scanning parameters, including field strength, number of gradients, and resolution. Thus, the variation in results between studies is likely, at least to some degree, attributed to these factors as well. Probabilistic high angular resolution tractography with individual delineating of the relevant tracts [Groeschel et al., 2014]—together with movement segmentation analysis—would be an interesting combination to apply to amplify our understanding of how the diffusion parameters relate to the underlying microstructural aberrations and to deviations in movement segmentation. This technique has some advantages compared with DTI-based tractography regarding tracking in high-density regions of crossing-fibers [Jones, 2010; Tournier et al., 2011], facilitating interpretation of the diffusion parameters in those areas in terms of the underlying microstructural alterations.

The selection of cohorts and analytical approaches, particularly regarding confounders, also varies between studies. Some studies exclude children with evidence of periventricular hemorrhage at birth or with ventriculomegaly [Constable et al., 2008; Mullen et al., 2011]. Age is a confounder regarding diffusion measures, but its effect is not always linear and varies across age in various parts of the brain [Snook et al., 2005]. We chose to include age as a linear covariate in the analysis of the diffusion measures as the E-PT group was younger than the other groups (although not significantly so), and the age effect was significant in the multivariate analysis.

A strength with this study is the division of the data based on preferred/non-preferred side rather than left/

right. This better reflects the development of the brain, as 10% of the sample (higher in children born PT) is non-right dominant, and it was a necessity for appropriate correlations with the movement segmentation data.

The present study is focused solely on upper-body movements. Deficits in upper-body and upper-limb movement control affect the efficacy and precision in reaching, grasping, and the fine manipulation of objects, thereby constraining the child's interaction with the environment [De Campos et al., 2009]. Upper-limb impairment is frequent (50%–70%) in individuals with cerebral palsy [Elvrum et al., 2012; Uvebrant, 1988]; a condition that is not only more prevalent in children with lower GA [Oskoui et al., 2013], but also, from a symptomatic viewpoint, can be deemed as the far end of the continuum of features that children born PT display [Pearsall-Jones et al., 2010]. Thus, in this realm, upper-limb movements are of particular importance to study.

CONCLUSIONS

This study provides evidence for the presence of subtle white matter impairments in brain areas important for motor control in children born extremely PT, and that these alterations are expressed as increased movement segmentation during goal-directed arm-hand movements. The findings give further understanding of the nature of the sensorimotor deviations commonly identified in children born PT. Moreover, they point toward the clinical importance of attending to sensorimotor development in this population during childhood, as subtle deviations often are present in otherwise healthy children. Further, early identification of problems with movement control allows preventative motor skill training, taking advantage of the young brain's plasticity to optimize motor function in children born PT at risk of suboptimal motor development.

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